REMARKS/ARGUMENT

This Amendment and Response Office Action dated July 16, 2003 is filed in conjunction with a Request for Continued Examination. In the Office Action certain claims stand rejected under 35 U.S.C. § 112, first paragraph; certain claims are rejected under 35 U.S.C. § 112, second paragraph; and all claims are rejected under 35 U.S.C. § 102(b) as anticipated by *Russell*.

REQUEST FOR EXAMINER INTERVIEW

Applicants respectfully request that the Examiner confirm a telephonic interview with the undersigned representative and Applicants, prior to further examination and issuance of an Office Action in this matter.

Withdrawal of Claim 42

Claim 42 is withdrawn in the Office Action as reciting a new SEQ ID NO: 16. In response, Applicants' point out that the synthetic peptide designated as SEQ ID NO: 16 has the same general sequence as SEQ ID NO: 4. Accordingly, claim 42 has been amended to recite SEQ ID NO: 4 instead of SEQ ID NO: 16. Rejoinder of Claim 42 is respectfully requested.

Objection to Claims over New Matter

In the Office Action of July 16, 2003 it is said that the recitation of "1-15 amino acids from the N- and/or COOH terminal of SEQ ID NO: 2 or 4 have been removed and 1 point mutation per each 10 amino acids of SEQ ID NO: 2 or 4, or portion thereof" are not disclosed either in the specification or in the originally presented claims. Cancellation of the allegedly new matter is required.

In reply, Applicants respectfully traverse the proposition that the indicated text which was added by amendment to claims 38-41 and 43-44 is not new. For example, at paragraph 54 of the specification guidance it is taught that 1 - 15 amino acids (*e.g.*, 1, 2, 3, 4, 5, 5-10, 10-15) are modified; and at paragraph 21 it is also taught that "1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 or more amino acids are deleted and inhibition [of activation of histidine kinase] measured." (Claims 38-41) It is clear that SEQ ID NO: 4 is a representative example of a fragment of SEQ ID NO: 2 in which residues 1-25 have been removed from SEQ ID NO: 2 and the fragment has competence signal peptide activity. Paragraph 53 of the specification teaches that a peptide with 90% identity to SEQ ID NO: 2 "may include up to 1 point mutation, such as substitutions with other amino acids, per each 10 amino acids of the referenced portion of the peptide in SEQ ID NO: 2 (Claims 43 and 44). As discussed in more

detail with respect to the § 112, 1st paragraph rejections, the claims are believed to be consistent with the 1999 USPTO's SYNOPSIS OF APPLICATION OF WRITTEN DESCRIPTION GUIDELINES currently published at http://www.uspto.gov/web/menu/written.pdf, Examples 13 and 14, in particular.

Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

Claim Rejections Under 35 USC § 112, First Paragraph

In the Office Action dated July 16, 2003, claims 22-28, 38-41 and 43-44 stand rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement in the specification. The Examiner acknowledges that the specification is enabling for an isolated polypeptide consisting of SEQ ID NO: 2 or 4. It is said that the specification lacks any evidence to show that the claimed fragments, variants or mimetic of SEQ ID NO: 2 or 4 would be able to confer genetic competence to S.mutans or confer acid tolerance response in *S.mutans* as measured by various assays neither have been constructed nor practiced in the present invention.

In reply, Applicants respectfully traverse for at least the reason that the disclosure gives instructions sufficient to enable a skilled person to obtain a range of polypeptides comprising CSP activity (see for example, Morgan and Gainor (1989) cited on page 15, paragraph [0056]. Given Applicants' disclosure, a person skilled in this technology at the time Applicants' invention was made would reasonably expect that a variety of polypeptides comprising all or part of SEQ ID NO: 2 or SEQ ID NO: 4 would possess at least some CSP activity. The specification contains directions enabling a person having ordinary knowledge and skill of the subject to make the invention described, without the exercise of undue experimentation. Likewise, guidance for designing modified CSP peptides is given in the specification at pages 16 - 17, paragraph [0063], and ways to screen such peptides as inhibitors of CSP are given in the specification on page 20, paragraphs [0072] - [0074]. Assays of genetic competence of the CSP peptide (SEQ ID NO: 4) are described on pages 22-23, paragraphs [0078] - [0079], and clearly establish how "[o]ne can identify compounds that inhibit CSP or variants thereof by adding a test compound to the mixture to determine if the quantitative measure of CSP stimulation is decreased by the addition of the test compound." Similarly, assays of acid resistance tolerance of CSP or variants thereof are described on pages 23-24, paragraph [0080]. The protocol for assaying a peptide for stimulatory/inhibitory effects on biofilm formation is described on page 25, paragraph [0085]. Analogous to the situation in Example 13, claim 1, of the SYNOPSIS OF APPLICATION OF WRITTEN DESCRIPTION GUIDELINES (discussed in more detail below), when taken in view of the general knowledge in the art, the disclosure is sufficient to show that one of skill in the art would conclude that Applicants were in possession of

the claimed genus. Thus, the skilled person would understand the limitations of the claims as written and would readily recognize whether a given polypeptide falls within or outside. To require the applicant to be limited to narrow claims directed only to SEQ ID NO: 2 and SEQ ID NO: 4 would unfairly deprive Applicants of embodiments to which they are entitled, and might give the Applicants' competitors an undeserved advantage.

The Office Action also takes the position that the added material in claims 38-41 and 43-44 is not supported by the original disclosure. In reply, Applicants respectfully traverse for the reasons discussed above under the subheading "Objection to Claims Over New Matter." Applicants have shown where support can be found in the specification as filed for the amendments to claims 38-41 and 43-44.

Claim 22 has been canceled in favor of incorporating its limitations into claim 24. Claim 24 specifically requires a peptide comprising all or part of SEQ ID NO: 2 or 4 and having competence signal peptide activity. Claim 23 is limited to comprising SEQ ID NO: 4. The wording of the currently amended claims is analogous to allowable Claim 1 of Example 13 (Protein Variant) and Example 14 (Product by Function) in the 1999 SYNOPSIS OF APPLICATION OF WRITTEN DESCRIPTION GUIDELINES currently published at http://www.uspto.gov/web/menu/written.pdf. In Example 13 of the Guidelines, claim 1 is drawn to "an isolated protein having SEQ ID NO: 3. The analysis of that claim provides,

> A search of the prior art indicates that SEQ ID NO: 3 is novel and nonobvious. The claim is directed to a genus of proteins that comprise SEQ ID NO: 3. One member of the genus, SEQ ID NO: 3, is described by a complete structure.
>
> There is relatively little variation among the species within the genus because each member of the genus shares SEQ ID NO: 3 as a necessary common feature. The single disclosed example is representative of the claimed genus because taken in view of the general knowledge in the art, the disclosure is sufficient to show that one of skill in the art would conclude that applicant was in possession of the claimed genus.

In Example 13 of the Guidelines, it is concluded with respect to claim 1 that the claimed subject matter is adequately described, and a rejection under the written description requirement should not be entered.

In the instant matter, SEQ ID NO: 4 is a subgenus of SEQ ID NO: 2 and as such is representative of the claimed genus (claim 23). Moreover, each member of the claimed genus must have competence signal peptide (CSP) activity.

With respect to claims 25, 38 and 43, and the claims which depend therefrom, Example 14 of the Guidelines is particularly analogous. The claim of Example 14 is drawn to "a protein having

SEQ ID NO: 3 and variants thereof that are at least 95% identical to SEQ ID NO: 3 and catalyze the reaction A → B." The analysis of the claim in Example 14 of the Guidelines states,

> A review of the full content of the specification indicates that a protein having SEQ ID NO: 3 or variants having 95% identity to SEQ ID NO: 3 and having catalytic activity are essential to the operation of the claimed invention. The procedures for making variants of SEQ ID NO: 3 are conventional in the art and an assay is described which will identify other proteins having the claimed catalytic activity. Moreover, procedures for making variants of SEQ ID NO: 3 which have 95% identity to SEQ ID NO: 3 and retain its activity are conventional in the art.
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> A review of the claim indicates that variants of SEQ ID NO: 3 include but are not limited to those variants of SEQ ID NO: 3 with substitutions, deletions, insertions and additions; but all variants must possess the specified catalytic activity and must have at least 95% identity to the SEQ ID NO: 3. Additionally, the claim is drawn to a protein which comprises SEQ ID NO: 3 or a variant thereof that has 95% identity to SEQ ID NO: 3. In other words, the protein claimed may be larger than SEQ ID NO: 3 or its variant with 95% identity to SEQ ID NO: 3. **It should be noted that "having" is open language, equivalent to "comprising".** The claim has two different generic embodiments, the first being a protein which comprises SEQ ID NO: 3 and the second being variants of SEQ ID NO: 3. There is a single species disclosed, that species being SEQ ID NO: 3.
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> A search of the prior art indicates that SEQ ID NO: 3 is novel and unobvious.
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> There is actual reduction to practice of the single disclosed species. The specification indicates that the genus of proteins that must be variants of SEQ ID NO: 3 does not have substantial variation since all of the variants must possess the specified catalytic activity and must have at least 95% identity to the reference sequence, SEQ ID NO: 3. The single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO: 3 which are capable of the specified catalytic activity. One of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus.
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> Conclusion: The disclosure meets the requirements of 35 USC § 112, first paragraph as providing adequate written description for the claimed invention.

In the instant matter, SEQ ID NO: 4 is a representative 21-AA fragment of the 46-AA SEQ ID NO: 2, and as such, has about 45% identity (homology), and possesses competence signal peptide activity. Moreover, "sequence identity" is defined in paragraph 53 of the specification: "[i]dentity refers to the similarity of two peptides or proteins that are aligned so that the highest order match is obtained. Identity is calculated according to methods known in the art, such as the ClustalW program." Based on the disclosure and the knowledge of a person of ordinary skill in the art, it will be apparent to such a person how to make and use the polypeptides and polypeptide fragments

characterized by SEQ. ID. NO: 2 or 4 by employing the Clustal W algorithm. Once the sequence identity of the sequences embraced by the present invention has been established the conclusion can be drawn that analogous function follows from sequence similarity. The representative active fragment SEQ ID NO: 4 shows that this is the case.

Claim Rejections Under 35 USC § 102(b)

With respect to claims 22-28, 38-41 and 43-44, the final Office Action maintains the previous rejection under 35 U.S.C. § 102(b) over U.S. Patent No. 4,521,513 (*Russell*). In the Office Action it is said, with respect to the *Russell* reference, "the disclosed protein inhibits the binding of CSP to *S.mutans* histidine because the protein (i.e., antigen or competent signal peptide) is from competent bacteria *S.mutans*, Inbritt strain and is used to prevent caries from bacteria *S.mutans* (see Column 4, lines 12-46)."Applicants respectfully traverse for at least the reason that a protein of unspecified sequence isolated from competent bacteria (*e.g.*, protein antigen C) does not necessarily include SEQ ID NO: 2 or 4. For example, there could be variations in growing conditions of the Inbritt strain of bacteria which might preclude expression of the claimed polypeptides. Moreover, it is reasonable to assume that a number of other proteins and polypeptides are isolatable from the bacterial cell membrane. Applicants strongly traverse the statement in the Office Action "Applicant agrees that the antigen disclosed by *Russell* is naturally competent." Applicants do not agree with that statement. Applicants agree that the Inbritt strain of *S.mutans* is competent and that a polypeptide of SEQ ID NO: 2 is naturally made in the Inbritt strain and others. It cannot, however, be reasonably assumed that any protein which can be used to prepare monospecific antisera, and which appears to be involved in the protection against dental caries afforded by vaccination with cell walls of *S.mutans* (col. 2, ll. 5-8), necessarily and inevitably includes SEQ ID NO: 2 or 4. Neither can it be assumed that the nature of its involvement in protecting against dental caries is exactly the same as that of SEQ ID NO: 2 or 4 (*e.g.*, competence signal peptide activity). New claims 47-56 illustrate such distinctions more particularly (*e.g.*, competence signal peptide (CSP) activity, inhibition of CSP activity, binding to histidine kinase receptor, promoting/inhibiting biofilm formation, promoting/inhibiting acid tolerance.

The MPEP § 2112 states that, if inherency is asserted, the Examiner must provide rationale or evidence tending to show inherency. More specifically,

> [i]n relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly

> inherent characteristic necessarily flows from the teachings of the applied prior art. *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990).

and

> [t]he fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art)

Applicants respectfully submit that there is insufficient factual basis to support the Office Action's proposition that SEQ ID NO: 2 and 4 are necessarily and inevitably present in the antigenic protein C, nor that the antigen of *Russell* possesses competence signal peptide activity. The Antigen C protein of the *Russell* publication is a 70kDa protein with an isoelectric point (pI) of 4.45 that functions as an immunogen to illicit an immune response when injected into monkeys. The CSP SEQ ID NO: 4 of the current invention is a 21 amino acid extracellular communications molecule with an estimated pI of 12.48 that is secreted by *S.mutans* and is detected by neighboring cells in a process called quorum sensing.

The Examiner states that with respect to the molecular weight and the pI of CSP that the "applicant is arguing the limitations which are not set forth in the claims". The Applicants respectfully submit that the molecular weight and the pI are mentioned to clearly show that the CSP and the ComC proteins of the current invention are not the prior art Antigen C protein. There is only one location for the CSP sequence in the *S.mutans* genome and it is in an open reading frame consisting of the comC gene, which encodes the CSP precursor protein, ComC. There is no other sequence in the *S.mutans* genome that, even when processed post translationally, can yield CSP. One of skill in the art, upon carrying out a routine search on the CSP sequence (SEQ ID NO: 4), and calculating typical parameters for that sequence, using well-known publicly available resources, would conclude that the Antigen C of the *Russell* publication does not inherently (or otherwise) comprise the CSP (SEQ ID NO: 4) or ComC (SEQ ID NO: 2) polypeptides of the claimed invention. Such publicly available resources and art-recognized parameters include NCBI database search, pI, molecular weight, hydrophobicity profiles, secondary structure predictions, charge distribution analysis, CLUSTALW pairwise alignment, protein composition analysis and stability predictions.

Claims 25-28 and 38-41, 43-44 recite variant or modified polypeptides which are clearly not disclosed in the *Russell* reference. New claims 45-57 further distinguish over the *Russell* reference.

Accordingly, Applicants believe that all of the pending and new claims distinguish over the cited references and fully comply with the requirements of 35 U.S.C. § 112. Entry of the foregoing

claim amendments, reconsideration of the rejections, and allowance of all claims are respectfully requested.

EXAMINER INTERVIEW SUMMARY

In mid September, 2003 the undersigned contacted the Examiner by telephone and requested a telephonic Examiner interview in which Applicants and their Canadian representative could participate. The 2-month response due date of September 30, 2003 was mentioned by the undersigned. At that time, the Examiner did not set a date for the interview due to the Examiner's heavy schedule through the end of September 2003. On October 3, 2003, the undersigned left a telephone message for the Examiner requesting an interview on a day not to include October 6 or 13. On October 6, 2003, the Examiner spoke with Willette Norman in the office of the undersigned, who indicated that the undersigned and Applicants could call the Examiner on October 14, 15 or 16. On October 13, 2003, the undersigned contacted Examiner Baskar by telephone to confirm a telephone conference on October 14, 2003. Although that conference was canceled due to a conflict in the Examiner's schedule, the Examiner indicated a willingness to schedule a conference at another mutually agreeable time. Applicants' continuing desire for a telephone interview with the Examiner via teleconference call, particularly to give Applicants' an opportunity to explain technical details of the invention, was noted. The Examiner offered suggestions for rewording claims 22 and 23. Claims 22-25 and the *Russell* reference were briefly discussed. No agreement was reached. The undersigned noted the 3-month deadline for response to office action on October 16, 2003, and stated that an amendment and response would be filed on or before that date and an interview with the Examiner would again be requested.

Conclusion

Applicants may have at times referred to claim limitations in shorthand fashion, or may have focused on a particular claim element. This discussion should not be interpreted to mean that the other limitations can be ignored or dismissed. The claims must be viewed as a whole, and each limitation of the claims must be considered when determining the patentability of the claims. Moreover, it should be understood that there may be other distinctions between the claims and the prior art, which have yet to be raised, but which may be raised in the future.

Consideration of the foregoing amendments and remarks, reconsideration of the application and withdrawal of the rejections and objections is respectfully requested by Applicants. No new matter is introduced by way of the amendments. It is believed that each ground of rejection and

objection raised in the Office Action dated July 16, 2003 has been fully addressed. If any item in the Office Action has been overlooked, Applicants respectfully request the opportunity to supplement this Response. A telephone interview with the Examiner prior to further examination and issuance of an Office Action is respectfully requested. Applicants believe that no extension of time is necessary for this paper to be deemed timely filed. If a petition for additional extension of time is necessary in order for this paper to be deemed timely filed, please consider this a petition therefor. If any fee is due as a result of the filing of this paper please appropriately charge such fee to Deposit Account Number 03-2769 of Conley Rose, P.C., Houston, Texas.

Respectfully submitted,

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